D8 wherein a sufficient amount of the therapeutic gene is expressed in human mammary carcinoma cells and the human mammary carcinoma is treated.

94. (Amended) A method for the treatment of human mammary carcinoma comprising

D9 administering to a human in need thereof a DNA construct comprising a therapeutic gene placed under transcriptional control of a rodent WAP regulatory sequence, wherein a sufficient amount of the therapeutic gene is expressed in human mammary carcinoma cells which results in treatment of the human mammary carcinoma.

REMARKS

Claim amendments

Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36-45, 47-94 are pending. Applicants have amended Claims 1, 13, 23, 26, 74, 79, 91 and 92 to recite a "retroviral vector comprising a heterologous gene placed under control of a MMTV U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template". . .. Support for the amendment can be found, for example, on page 5, lines 13-15, Example 2 and Figure 5 of the specification. Claims 37-40, 70-73, 92 and 94 have been amended to recite the essential steps of the claimed methods. Support for the amendment can be found, for example, in Example 5. No new matter has been introduced.

Rejection of Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36, 38, 44, 45, 55-57, 62, 66, 74-81, 84, 91 and 92 under 35 U.S.C. §112, second paragraph

Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36, 38, 44, 45, 55-57, 62, 66, 74-81, 84, 91 and 92 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 2). The Examiner states that "it is unclear what nucleotide

sequence is intended for the phrase 'U3 region of MMTV' or '0.6 Kb PstI MMTV promoter fragment'" (Office Action, page 3).

Applicants respectfully disagree. Nevertheless, Applicants have amended Claims 1, 13, 23, 26, 74, 79, 91 and 92 to recite a "retroviral vector comprising a heterologous gene placed under control of a MMTV U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template". . .. Support for the amendment can be found, for example, on page 5, lines 13-15, Example 2 and Figure 5 of the specification.

The Examiner further states that "Applicants argue that WAP promoter is well known in the art" but that "[t]his is not found persuasive" (Office Action, page 3). Applicants assume that the Examiner is maintaining that the phrase "proximal 445 bp of the murine WAP promoter in Claims 44" is vague and indefinite (Office Action, dated November 21, 2000, page 3), since "[m]urine WAP encompasses promoter sequences derived from various murine sequences" (Office Action, dated November 21, 2000, page 3). Applicants also assume that the Examiner is maintaining that the phrase "320 bp XhoI/XbaI of the murine WAP promoter" is vague and indefinite (Office Action, dated November 21, 2000, page 3).

Applicants respectfully disagree. Applicants clearly teach in the specification as filed that "the region of the WAP promoter which is required for mediating the mammary gland specificity is a 320 bp XhoI\XbaI restriction fragment (-413 to -93)" and cite a specific reference in support thereof *i.e.*, Kolb, A.F. *et al., Biochem. Biophys. Res. Comm., 217:*1045-1052 (1995) (specification, page 11, lines 17-19). Applicants direct the Examiner's attention to the Kolb *et al.* reference which was filed as Reference AR in the Information Disclosure Statement mailed to the U.S. Patent Office on March 16, 1999. Specifically, Applicants direct the Examiner's attention to Figure 1 of Kolb *et al.* which clearly shows the "[s]tructure of the proximal region of the WAP promoter", "[i]mportant restriction sites" such as a "320bp XhoI/XbaI restriction fragment (-413 to -93)" (Kolb *et al.*, Figure 1 legend). Thus, the phrases "proximal 445 bp of the murine WAP promoter" and "320 bp XhoI/XbaI of the murine WAP promoter" are definite.

As amended, the claims are definite and particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Rejection of Claims 37-40, 70-73, 92 and 94 under 35 U.S.C. §112, second paragraph

Claims 37-40, 70-73, 92 and 94 are rejected under 35 U.S.C. §112, second paragraph "as bing incomplete for omitting essential steps, such omission amounting to a gap between the steps" (Office Action, page 3).

Claims 37-40, 70-73, 92 and 94 have been amended to recite the essential steps of the claimed methods. Support for the amendment can be found, for example, in Example 5.

Rejection of Claims 1, 2, 9-14, 16-19, 23-28, 31-33 and 36-94 under 35 U.S.C. §112, first paragraph

Claims 1, 2, 9-14, 16-19, 23-28, 31-33 and 36-94 are rejected under 35 U.S.C. §112, first paragraph because the specification "does not reasonably provide enablement for any retroviral vector comprising any therapeutic gene under the control of a MMTV promoter or a WAP promoter and said therapeutic gene is expressed in a cell *in vivo*, a method of expressing said therapeutic gene in a human cell *in vivo*, any pharmaceutical composition comprising a DNA construct comprising any therapeutic gene under the control of a MMTV promoter or a WAP promoter, and a method for the treatment of human mammary carcinoma comprising administering to a human a retroviral particle expressing any therapeutic gene under the control of a MMTV or WAP promoter *in vivo*" (Office Action, page 4).

Applicants respectfully disagree. As pointed out in the previously filed Amendment, in the specification as filed, Applicants show how to make a retroviral construct in which β-gal is placed under the transcriptional control of a WAP or a MMTV regulatory region (Examples 1-3); how to make retroviral particles produced by culturing a packaging cell line harboring the retroviral vector and one or more constructs coding for proteins required for the retroviral vector to be packaged (Example 4); and how to infect mammary cells using supernatant containing the retroviral particles *in vitro* (Example 4). Applicants also show methods for assessing whether the WAP or MMTV-U3 regulatory sequence drives expression of a heterologous gene within a vector in human cells, such as primary human mammary gland cells (specification, pages 30-31). Applicants further describe how to make a retroviral vector carrying the cytochrome P450 gene, a therapeutic gene which encodes a protein that catalyses the hydroxylation of the commonly used cancer prodrugs CPA and ifosfamide to their active toxic forms, under control of the WAP

regulatory sequence; how to encapsulate a packaging cell line containing the claimed construct and how to implant the capsules which produce viral particles in or around mammary tissue to ensure continuous release of virus *in vivo* (Example 5).

It is well known in the art that the structure and life cycle are highly conserved among retroviruses. The sequence of numerous therapeutic genes, in addition to the examples of therapeutic genes Applicants provide in the specification (*e.g.*, page 7, line 22 - page 8, line 2), are also well known in the art. One of skill in the art can obtain a known gene and insert the gene (*i.e.*, a heterologous gene such as a therapeutic gene) into a retroviral vector using well known techniques (*e.g.*, techniques using restriction enzymes or PCR technology). For example, a person of skill in the art can obtain a known gene from a commercial source or use known restriction enzymes to obtain or isolate the gene. Known restriction enzymes can also be used to open the retoviral vector in combination with other known enzymes (*e.g.*, ligases) to then insert the gene into the retroviral vector. Alternatively, PCR technologies can be used with genes or DNA sequences in which only a portion of the sequence is known. The portion of the known sequence is used as primer binding sites to amplify the sequence between the primer binding sites which allows for determination of the entire sequence of the gene. Once the sequence is determined, the sequence can be inserted into a retroviral vector as described above. Thus, to obtain or isolate a gene using commercial sources, restriction enzymes or PCR technologies followed by ligation of the gene with a retroviral vector backbone are routine methods to those of skill in the art (*e.g.*, see Sambrook *et al., Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, 1989).

It is also well known in the art that retroviral vectors function according to one main principle, *i.e.*, they exploit the cellular machinery for their own propagation. That is, retroviral vectors stably integrate their genome into the cellular genome of an infected cell during its life cycle. Retroviruses propagate their genomic information by transcribing their RNA genome into a proviral DNA, which is then integrated into the genome of the infected cell. As soon as the retroviral genome is integrated into the genome of the infected cell, it will behave like a cellular gene, and thus, be expressed. Thus, they are excellent vectors for introducing long-term expression of various genes in target cells. Accordingly, Applicants demonstration that a MLV retroviral vector comprising a WAP or MMTV regulatory region can generate a retroviral particle

which infects living cells, that the retroviral vector can integrate the incorporated heterologous gene into the genome of the target cell and can induce expression of the introduced heterologous gene in primary human mammary cells, including human mammary carcinoma cells, is provides sufficient enablement of Applicants' claimed invention.

Finally, the general feasability of the *in vivo* use of retroviral vectors to treat a disease is well accepted in the art and it is universally accepted by those of skill in the art. For example, Blaese, *et al.* (Exhibit 1: *Science* (1995) 270: 475-480), disclose a clinical trial involving retroviral-mediated transfer of the adenosine (ADA) gene into the T-cells of two children with severe combined immune deficiency (ADA-SCID). In this example of gene therapy, upon treatment the number of T-cells normalized, as did many cellular and humoral immune responses. In a further example, Bordignon *et al.* (Exhibit 2: *Science* (1995) 270: 470-475) also used a retroviral vector for the same purpose as Blaese *et al.* and received similar results. In yet a further example, Grossman *et al.* (Exhibit 3: *Nature Genetics* (1994) 6: 335-341) report successful *ex vivo* human gene therapy directed to the liver of a patient with familial hypercholersterolaemia.

Thus, undue experimentation is not required to practice Applicants' claimed invention. That is, using the guidance provided by Applicants in the specification as filed and the knowledge in the art, a person of skill in the art is fully enabled to handle, propogate and modify retroviruses other than the MLV vector Applicants used to exemplify the invention, in order to obtain retroviral vectors comprising a heterologous gene placed under transcriptional control of a MMTV or WAP regulatory region. Furthermore, using routine experimentation and the guidance Applicants provide in the specification, one of skill in the art can use Applicants' claimed vectors to express the heterologous gene *in vitro, ex vivo* or *in vivo* in human cells, for example, to treat human mammary carcinoma.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

<u>Rejection of Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36, 74-81, 91 and 92 under 35 U.S.C. §103(a)</u>

Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36, 64-81, 91 and 92 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Dranoff et al., 1993 (U2) in view of Lefebvre et al., 1991

(V2), Wilson et al., 1995 (X3), Archer et al., 1994 (U4), Gunzburg et al. WO 96/07748 (IDS-AQ) and Shao et al., 1994 (X2)" (Office Action, page 7).

The Examiner maintains that the priority document "only discloses the use of U3-R-U5 structure that has the U3 region completely or partially deleted and replaced by polylinker containing WAP or MMTV regulatory sequence at **both** 5'LTR and 3' LTR" and that the "claimed invention is directed to the use of **intact** U3-R-U5 at the 5'LTR region and a 3' LTR region comprising a completely or partially deleted U3 region and replaced by a polylinker containing MMTV regulatory sequence" (Office Action, pages 7-8). The Examiner concludes that "the claimed invention is not supported by the specification of the foreign publication, Denmark 0976/95" (Office Action, page 8). The Examiner further states that the "specification fails to disclose the use of a 0.6 Kb PstI MMTV promoter fragment . . ." and further concludes that "the claimed invention is not supported by the specification of the foreign publication, Denmark 0976/95" (Office Action, page 8).

Applicants respectfully disagree. Nevertheless, as noted above, the claims have been amended to delete the phrase "0.6 Kb PstI MMTV promoter fragment", and to recite a retroviral vector comprising a heterologous gene placed under control of a MMTV U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template, wherein the MMTV U3 sequence directs expression of the heterologous gene in a human cell when the vector is introduced into the cell. Furthermore, the Examiner's comparison of the priority document's teaching of "the use of U3-R-U5 structure that has the U3 region completely or partially deleted and replaced by polylinker containing WAP or MMTV regulatory sequence at **both** 5'LTR and 3' LTR" with the subject application's teaching of "the use of **intact** U3-R-U5 at the 5'LTR region and a 3' LTR region comprising a completely or partially deleted U3 region and replaced by a polylinker containing MMTV regulatory sequence" is only a comparison of two different stages in the life cycle of a retrovirus. As discussed below, due to the life cycle of a retrovirus, "the use of **intact** U3-R-U5 at the 5'LTR region and a 3' LTR region comprising a completely or partially deleted U3 region and replaced by a polylinker containing MMTV regulatory sequence" results in "the use of U3-R-U5 structure that has the U3 region completely

or partially deleted and replaced by polylinker containing WAP or MMTV regulatory sequence at **both** 5'LTR and 3' LTR".

An explanation of the retroviral life provided below shows that the subject invention is indeed supported by the specification of the priority document, Denmark 0976/95. The RNA genome of a retrovirus has the structure:

R-U5-body-U3-R.

During reverse transcription the U3 and the U5 regions are duplicated forming a proviral DNA with the structure:

U3-R-U5-body-U3-R-U5.

The proviral DNA is then integrated into the cellular genome. Since the transcription start site is at the beginning of the 5' region while the poly[A] is at the end of the 3' R region, any resulting retroviral RNA genome has the structure:

R-U5-body-U3-R.

It is obvious to the skilled person that it is cumbersome to work with and modify an RNA molecule. Accordingly, techniques for constructing or modifying retroviruses work with a retroviral DNA molecule. If the 3' U3 region is modified in the DNA molecule, a modified DNA molecule with the following structure arises:

U3-R-U5-body-modified region-R-U5.

Since cloning techniques generally involve the use of plasmids, this DNA molecule is present in a standard plasmid, which can be amplified and also transfected to a target cell. This target cell will under certain conditions, particularly under selection pressure, integrate this modified DNA molecule into its genome. After this integration and driven by the promoter element in the U3 region a modified retroviral RNA genome is transcribed having the structure:

R-U5-body-modified region-R.

This modified RNA genome is packaged into a particle and will, after infection (in the next round of reverse transcription) form a newly but modified proviral DNA molecule having the structure:

modified region-R-U5-body-modified R-U5.

It is clear that if the 3' LTR is modified as described in the subject application, after only one round of infection the proviral will comprise two modified LTRs. Thus, the priority document discloses the same as the subject application and consequently, priority to 0976/95 must be

acknowledged. Thus, the Gunzburg *et al.* reference, which was published after Applicants' priority date, is not prior art to Applicants' claimed invention.

The remaining references do not render obvious Applicants' claimed invention. Dranoff *et al.* used the ***Mo-MuLV LTR*** to generate "10 retroviruses encoding potential immunomodulators and studied the vaccination properties of murine tumor cells transduced by the viruses" (Dranoff *et al.*, abstract). Lefebvre *et al.* identified two regions of the MMTV LTR that regulate its promoter activity in ***murine*** cells, but do not teach or even suggest that the MMTV promoter can be used to express a heterologous gene in a human cell. Archer *et al.* use the ***human cell line***, T47D(A1-2), which contains the MMTV promoter stably integrated and which expresses comparable levels of glucocorticoid and progestin receptors (Archer *et al.*, page 1155, column 1). Wilson *et al.* describe pMTV-D305, "a ***hybrid plasmid vector*** that contains the bacterial neomycin-kanamycin resistance genes neo and an altered SV40 early region coding for the SV40 large T antigen, but not the small Y antigen, under the control of the mouse mammary tumor virus promoter that is positively regulated by corticosteroids" (Wilson *et al.*, page 33, column 1). Shao *et al.* encapsulated GM-CSF-secreting cells in semi-permeable microcapsules (Shao *et al.*, page 59, column 1), demonstrating "the merit of this cell encapsulation system" (Shao *et al.*, page 60, column 1). Shao *et al.* do not discuss use of the MMTV or WAP regulatory sequences for any purpose.

The combined teachings of the references clearly do not teach or suggest a retroviral vector comprising a heterologous gene placed under control of a MMTV U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template or that such a retroviral vector could be used to direct expression of the heterologous gene in *human* cells. Dranoff *et al.* and Shao *et al.* do not even mention the MMTV promoter or the use thereof for any purpose. Lefebvre *et al.*, Archer *et al.* and Wilson *et al.* discuss the MMTV LTR but do not teach or even suggest using the MMTV LTR in a retroviral vector to direct expression of a heterologous gene in a human cell.

As pointed out in the previously filed Amendments, where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out

the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* The court has clearly stated that

> [a]n invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. . . Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art. . . The critical inquiry is whether 'there is something in the prior art as a whole to *suggest* the desirability, and thus obviousness of making the invention' (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*13 USPQ2d 1737 at 1765).

That is, the issue is "whether the teachings of the prior art would, *in and of themselves and without the benefit of appellant's disclosure,* make the invention as a whole, obvious" (*In re Sponnoble* 160 USPQ237 at 243 (CCPA 1969)).

The Examiner has not established that there is something in the prior art as a whole to *suggest* the desirability, and thus obviousness of making the invention. Applicants maintain that the prior art combination of record has been made with the impermissible advantage of hindsight, and thus, the rejection is legally improper. That is, in making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicant's disclosure in which there is a clear teaching of a retroviral vector comprising a heterologous gene placed under control of a MMTV U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template and that such a retroviral vector could be used to direct expression of the heterologous gene in *human* cells. As the court made clear in *In re Dow*, it is not legally correct to rely on Applicant's disclosure for the suggestion that the cited references should be combined and the expectation of success. In the present case, the suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The teachings of Dranoff *et al.* in view of Lefebvre *et al.*, Wilson *et al.*, Archer *et al.*, and Shao *et al.* do not render obvious Applicants' claimed invention.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Four times amended) A retroviral vector comprising a heterologous gene placed under transcriptional control of a [0.6 Kb PstI] MMTV [promoter fragment] U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template, wherein the MMTV [promoter fragment] U3 sequence directs expression of the heterologous gene in a human cell when the vector is introduced into the cell.

13. (Three times amended) A retroviral provirus carrying a construct comprising a heterologous gene placed under transcriptional control of a [0.6 Kb PstI] MMTV [promoter fragment] U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template, wherein the MMTV U3 sequence directs expression of the heterologous gene in a human cell when the vector is introduced into the cell.

23. (Three times amended) A pharmaceutical composition comprising a DNA construct comprising a therapeutic gene placed under transcriptional control of a [0.6 Kb PstI] MMTV [promoter fragment] U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template, wherein the MMTV U3 sequence directs expression of the heterologous gene in a human cell when the vector is introduced into the cell, and a pharmaceutically acceptable carrier or diluent.

26. (Four times amended) A method for the expression of a heterologous gene in a human cell comprising introducing a retroviral vector comprising said gene under transcriptional control of a [0.6 Kb PstI] MMTV [promoter fragment] U3 sequence homologous to a PCR

amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template into the human cell and maintaining the cell under conditions in which the gene is expressed in the human cell.

37. (Three times amended) A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a DNA construct comprising a therapeutic gene placed under transcriptional control of an MMTV regulatory sequence, wherein a sufficient amount of the therapeutic gene is expressed in human mammary carcinoma cells [and] which results in treatment of the human mammary carcinoma [is treated].

38. (Twice amended) A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a viral particle according to claim 12, wherein the viral particle infects human mammary carcinoma cells in the human and the heterologous gene is expressed in a sufficient amount that results in treatment of the human mammary carcinoma .

39. (Three times amended) A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a cell line containing a DNA construct comprising a therapeutic gene placed under transcriptional control of an MMTV regulatory sequence, wherein a sufficient amount of the therapeutic gene is expressed in human mammary carcinoma cells [and] which results in treatment of the human mammary carcinoma [is treated].

40. (Twice amended) A method for the treatment of human mammary carcinoma comprising implanting into a human in need thereof either in or nearby the site of the tumor a capsule encapsulating a cell line containing a construct comprising a therapeutic gene placed under transcriptional control of an MMTV regulatory sequence, said capsule comprising a porous

capsule wall surrounding said cell line, said porous capsule wall being permeable to a heterologous polypeptide encoded by the gene or the viral particles produced by said cells, wherein a sufficient amount of the heterologous polypeptide is expressed in human mammary carcinoma cells [and] which results in treatment of the human mammary carcinoma [is treated].

70. (Twice amended) A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a DNA construct comprising a therapeutic gene placed under transcriptional control of a WAP regulatory sequence, wherein a sufficient amount of the therapeutic gene is expressed in human mammary carcinoma cells [and] which results in treatment of the human mammary carcinoma [is treated].

71. (Amended) A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a viral particle according to claim 60, wherein the viral particle infects human mammary carcinoma cells in the human and the heterologous gene is expressed in a sufficient amount that results in treatment of the human mammary carcinoma.

72. (Amended) A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a cell line containing a DNA construct comprising a therapeutic gene laced under transcriptional control of an WAP regulatory sequence, wherein a sufficient amount of the therapeutic gene is expressed [and] which results in treatment of the human mammary carcinoma [is treated].

73. (Amended) A method for the treatment of human mammary carcinoma comprising implanting into a human in need thereof either in or nearby the site of the tumor a capsule encapsulating a cell line containing a construct comprising a therapeutic gene placed under transcriptional control of an WAP regulatory sequence, said capsule comprising a porous capsule wall surrounding said cell line, said porous capsule wall being permeable to the heterologous polypeptide or the viral particles produced by said cells, wherein a sufficient

amount of the heterologous polypeptide is expressed in human mammary carcinoma cells which results in treatment of the human mammary carcinoma.

74. (Twice amended) A retroviral vector comprising a heterologous gene placed under transcriptional control of a [0.6 Kb PstI] MMTV [promoter fragment] U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template, wherein the MMTV [promoter fragment] U3 sequence directs expression of the heterologous gene in a human mammary cell when the vector is introduced into the cell.

79. (Twice amended) A retroviral provirus carrying a construct comprising a heterologous gene placed under transcriptional control of a [0.6 Kb PstI] MMTV [promoter fragment] U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template, wherein the MMTV U3 sequence directs expression of the heterologous gene in a human mammary cell when the vector is introduced into the cell.

91. (Twice amended) A method for the expression of a heterologous gene in a human cell comprising introducing a retroviral vector comprising said gene under transcriptional control of a [0.6 Kb PstI] MMTV [promoter fragment] U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV provirus as PCR template into the human cell and maintaining the cell under conditions in which the gene is expressed in the human cell.

92. (Twice amended) A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a DNA construct comprising a therapeutic gene placed under transcriptional control of a [0.6 Kb PstI] MMTV [promoter fragment] U3 sequence homologous to a PCR amplification product obtainable by the primers D (SEQ ID NO: 4) and E (SEQ ID NO: 5) and a MMTV provirus or a plasmid comprising a MMTV

provirus as PCR template, wherein a sufficient amount of the therapeutic gene is expressed in human mammary carcinoma cells and the human mammary carcinoma is treated.

94. (Amended) A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a DNA construct comprising a therapeutic gene placed under transcriptional control of a rodent WAP regulatory sequence, wherein a sufficient amount of the therapeutic gene is expressed in human mammary carcinoma cells [and] which results in treatment of the human mammary carcinoma [is treated].